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Date: Mon, 26 Jun 2000 14:15:41 -0800
To: Joshua Lederberg <jsl@jl10.rockefeller.edu>
From: Garry Hamilton <gbhamilton@seanet.com>
Subject: Re: interview request -- [[re microbiome

Dr. Lederberg:

Here is a transcript of our recent discussion. If you would like to elaborate on any point after reading it, please do. If you don't mind, I may also have a follow-up question or two.

Many thanks once again for your time.

Sincerely,

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JL: The bugs are schizophrenic because they don't know whether to kill us or harvest us, so we have to be schizophrenic in trying to cope with those diverging tendencies.

Q: What about Typhoid Mary? Why didn't she get sick and why did only a small number of people she would have come into contact with become ill?

We don't know very much about those individual variations. One very likely distinction is what previous exposure and immunity various people had, including herself. She obviously had reached some kind of equilibrium with the organism that was sequestering itself in her gall bladder. That's the traditional place for carriers of typhoid. So they lived happily together.

Q: The fact these questions remain unanswered-does this reflect our current view of germs and how we tend to focus entirely on pathogens and virulence?

Well, not entirely but it's much more difficult to study carrier states. They last a long time, they're hard to reproduce in animal models and the question 'what experiment would you do next?' can be

a rather perplexing one. For whatever reason there certainly is much less known about this carrier state than about acute infection. Chronic disease falls somewhere in between.

Q: You talk about a shift from a war metaphor to an ecology perspective. Does this include the micro ecology of the individual?

Oh yes, In fact that's really my main focus. Subsequent to that Science article I've been introducing the expression 'microbiome' and it's at par with the genome and the chromosomes and the chondriome, which is the piece of our genome which is in mitochondria, to try and emphasize that there is a very large packet of other genes that we carry around with us habitually. Now they're not transmitted as regularly and as mechanically as the chromosomes are, but that doesn't lessen their importance. Do your gut flora influence your personality? I'd be inclined to guess they do. There's no evidence on that score. It's, again, not studied. There is a very large literature on the endosymbiosis. There's no question about the essentiality of these symbionts for the nutrition of almost any insect you care to name.

Q: We've treated this part of our superorganism pretty poorly?

Well, we haven't investigated it very thoroughly.

Q: But also with our attack on germs and the side-effects this might have.

Q: Well, that's exactly right and we come to grief sometimes, most notoriously with *Clostridium difficile* infections. That's the outstanding example.

Q: Those are short-term disruptions. Do you worry we may be causing more permanent damage to our superorganism?

We grew up many thousands, if not tens or hundreds of thousands of years, in an uneasy equilibrium where we had a pretty extensively contaminated environment. I don't want to say it compares to the sewage of a modern city but nothing was known about hygiene and there was not great care about where to put human waste and so forth for many thousands of years. So we were beset by constant antigenic stimulation which gave us some small degree of herd immunity, which resulted in maternal immunity which is transmitted to the offspring and now that equilibrium is broken when we have better hygiene and the best manifestation of it is the history of epidemic poliomyelitis. Now I'm not sure I totally believe that

explanation. It seems okay. It's not been directly investigated and I don't know to what extent genetic and evolutionary change in the polio virus itself might have accounted for that, or the two together, the ecological and evolutionary effect. I think when we do a genomic analysis we're going to find that the prime mover may have been some immediate change in ecologic relationship, but that sets in force selective factors that are going to bring certain genotypes to the fore compared to what we had before, so you'll be likely see changes in both sides.

Q: If you have a niche in your body wouldn't you want it filled with something that has been with us for thousands of years rather than some Johnny-come-lately?

I would guess so but not with tuberculosis. There are some pretty bad actors that have managed to get in there, too, and aren't bad enough to be lethal but bad enough to make you pretty miserable. Even if you assume that it's in the bug's interest to keep the host alive, it's not to keep the host alive, well, ticking and in robust health. Something a little less than that may be more nearly the bug optimum. And, also not to be forgotten, this is why you end up being schizophrenic: a three percent case fatality rate for a human disease is horrendous. For the bug it's a three percent reduction in fitness by killing the host. So that doesn't matter much. We have to view these as very vague growth trends, not sharply honed to meet our very specific human requirements.

Q: You've written: "too much antibacterial zeal could wipe out the very immunogenic stimulation that has enabled us to live with microbes in the first place." Is there a line we need to draw?

I don't know. I think the cleaner the better provided you substitute known dirt for the unknown dirt. And provided you know enough to know what to put in that dirt. You could exclude the ranker pathogens and keep the more benign. I think nature offers us something in between. I don't believe nature is benign at all. It's indifferent. It's amoral. So the fact that something is natural doesn't mean that we ought to embrace it. But it ought to give us some lessons about what to look for and what to avoid.

Q: Are we not now in our current approach trying to replace bad dirt with no dirt?

That's right and that's a sweeping-clean, ethnic-cleansing kind of military metaphor. I try more of a political one: have friends rather than enemies populate that space and try to do it with the least bloodshed possible on all sides.

Q. But biologically speaking, nature abhors a vacuum. Is that not something we should be worried about?

Yes, I think that's quite appropriate here. A (?) not already populated with microbes is going to be in very short order.

niche

Q: An ecology of body will have to start taking into account stress, hormones, cytokines?

Of course. Although I think diet plays a very large role. It occurred to ~~be~~ in thinking about nutraceutical immunogens, we haven't polled the existing variety of diet to see if any of them are already doing part of that job. It could be right under our noses and we don't know it.

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any microbes

Q: Do you think we've overestimated virulence and underestimated things like diet? One study from Bangladesh showed that babies dying of enteric infections carried the same organisms as those who were not.

← how thoroughly

You could find support on both sides. With enteric disease that's certainly the case. We don't have many babies in this country dying of diarrhoea, yet that's a very common cause of death in nutritionally deprived countries, probably via the immune system although what part of it and exactly how isn't completely clear. On the other hand, something like the flu in 1918. It was totally non-discriminating. It hit healthy young men by the droves.

Q: Do we know what role social disruption played in that epidemic?

← mobility.

I don't think, if you read the contemporary history, it had a lot to do with the spread. There were people from every walk of life. I don't think you can see much social history in that story. I don't know what Crosby had to say.

A.W.

Q: But have we overestimated the role of hygiene and underestimated the role of other factors?

I don't know about under-estimated. I think we may have mis-estimated it. Hygiene accounts for a very, very large large part of our improvement in health status in the first 50 years of the century. Certainly all the epidemics of water-borne disease, I don't want those back again. I don't think we've overestimated it there. I think that is the big part of the story, we just don't have typhoid fever anymore in this country. And I think that can be placed almost entirely on cleaning up the water supply. Other

factors will come into play for other diseases.

Q: You've written about HIV: "our focus on extirpating the virus may have deflected less ambitious, though more pragmatic aims, including learning to live with the virus by nurturing in equal measure, the immune system that HIV erodes."

We don't know why HIV is so nasty in humans when there's a whole family of similar viruses in monkeys that don't do anything of the kind. That are relatively benign if they even cause disease at all.

Q: What kind of reaction did your essay in Science receive?

An amazing one. Fairly undifferentiated; people saying they thought it was an eye-opener and that they learned a lot from it, and very congratulatory. I didn't get much detailed critical response. I think a lot of people are still digesting the messages it has to offer. I've been a little critical of it. I didn't emphasize the schizophrenic aspects of it sufficiently. The general tone of it is too much on the side of the benign behaviour of the bugs. I back off that a little bit. As I said, it's a matter of perspective. That three percent case fatality means one thing~~s~~ to the bugs and another thing to us.

Q: But what about the other factors besides virulence? No, I'll stand by and reinforce what I said about the narrowness of our research agenda. But, you know, first things first. You have to find what the toxins were, then figure out ~~why~~ they're there and how they're modulated. One thing that brought this home to me was pondering where we find the most poisonous toxins. The one that is most grievous by far is botulinus. You don't find that in any systemic infection and if it were ever to find its way into a staph or strep, God help us, although it probably wouldn't spread very far, because it would be lethal at a very early stage. People would drop dead and not transmit it any more. It's evidence, but it's not a very hard reductionist story, it's just building a case for thinking more about this in our research agenda.

in the population

Q: You've mentioned the examples of polio and hepatitis. Do you view it that if these organisms can get into a host early they behave one way, but if they're blocked out they behave another way?

If they've gotten in early it sets in motion a cycle of events in which host immunity is undoubtedly ~~apart~~. It may be more to it than that in that there's a different manifestation of the disease

regardless of the immune status at different ages, but we're treading on pretty thin ice, we just don't know. It looks like that has to be the case, too, but very little direct evidence.

Q: If an organism is benign when it is ubiquitous, is there not a danger in disrupting that ubiquity?

That comes to the fore in the discussion about eradication of disease as the extreme example. I think we're putting ourselves in very dangerous situation, having completed the eradication of small pox and going on to polio and not having a strategy to cope with, what if? what if it comes back and you have a totally sensitive human herd? It will be unlike anything in history.

Q: Is this what you meant by "cleaner is not always better if we don't have the street smarts to respond to new challenges'?"

That's the most acute example of it. I had in mind much more broadly that the overall status of the immune system may be compromised by not having sufficiently varied stimulation.

Q: Are we ready for this intellectual shift?

I think so. A lot of people have been supportive. I've been more critical than some of the other folks. I think that I may have carried it a little too far, at least it's susceptible to misunderstanding. It's a very complicated story to try to get over. I don't want to be too dismissive about being clean. I think it's been very important that we have coped with a variety of infections. I don't want to rely too much on the benign outcome of our chronic association. I think bugs from time to time turn right back and lash back very, very savagely. We need to be playing the game on both sides of the street-the bug as a militant attacker and the bug as a symbiont, just be very vigilant that we understand the balance between those two ways of life. A lot of genomic analysis is needed in order to discriminate different strains of bugs that behave differently and much more subtle examination of the context in which disease occurs and which may modify disease outcome.

Q: What do you you think of the hygiene hypothesis?

for asthma.

It needs to be entertained. It's not a very solid case. The distribution of asthma is much higher in the inner cities than it is in the more affluent areas and this might lead you to think the opposite. But it's certainly something that needs to be examined. What we can do is do much more detailed profiling of what actually is in our "immunome."